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14. ABSTRACT

This is a study of the effects of ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), on the osteogenic response to 9 months of exercise training in healthy, premenopausal women, aged 21 to 40 years (N=102). The hypotheses are:
$H1_a$: taking short-acting NSAIDS before exercise will diminish increases in bone mineral density (BMD) in response to exercise training
$H1_b$: taking short-acting NSAIDS after exercise will not diminish the increases in BMD in response to exercise training
Participants take either ibuprofen (400mg) or placebo capsules before and after each exercise session. Women are randomized to three treatment arms: 1) NSAID before exercise, placebo after exercise (NSAID/placebo; n=34); 2) placebo before exercise, NSAID after exercise (placebo/NSAID; n=34); and 3) placebo before exercise, placebo after exercise (placebo/placebo; n=34). One hundred thirteen women completed baseline testing and were randomized to treatment; 62 women have completed the study. Final follow-up testing and sample analyses will be completed in the next 4-5 months. These studies could lead to the development of new strategies to reduce the incidence of, and treatment for, stress fractures that occur in response to vigorous physical activity.

15. SUBJECT TERMS
Exercise, stress fracture, ibuprofen, prostaglandins, bone mineral density, estrogen

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INTRODUCTION:

The primary aim of this randomized, double-blinded, placebo-controlled trial is to determine the effects of NSAID (ibuprofen) use on the osteogenic response to 9 months of exercise training in 102 women. The scientific rationale for this study centers on the knowledge that the osteogenic response to mechanical stress is a prostaglandin (PG)-dependent process and that NSAIDs inhibit PG synthesis. There is evidence that regular NSAID use inhibits the normal bone formation response to mechanical loading, increases risk of fracture, and impairs bone healing. The approved statement of work for this project includes 4 years of recruiting, testing, and training subjects as well as completing sample assays, data analysis, and manuscripts.

BODY:

The original objectives for year 4 were to complete all follow-up tests, procedures, and biochemical assays, perform data analyses, and prepare manuscripts. We are approximately 6 months behind in meeting these goals, due, in part, to the delayed start of the project. Although the date of award was September 20, 2001, there was a stipulation that work could not commence until IRB and HSRRB review and approval processes were completed. The fully executed agreement was signed on January 31, 2002. Another unexpected delay occurred as a result of the relocation of the PI's laboratory. Because of these delays, the PI requested, and was granted, a one-year no-cost extension of the award period to complete the project.

Enrollment of study participants was completed in May 2005. The original targeted enrollment (N=102) was increased by ~10% because the attrition rate was slightly higher than predicted (28% vs 25%). Figure 1 illustrates the flow of volunteers through the study. As of September 2005, 62 participants had completed the study and 19 remained active in the protocol. Based on the power analyses in the grant proposal, we need 19 finishers per group (N=57) to achieve 80% power and 25 finishers per group to achieve 90% power. We are on track to meet the required number of finishers. The racial and ethnic characteristics of the study participants are similar to those that were projected, which reflect the demographics of the Denver metropolitan area (Table 1).

Body composition and bone mass data have been analyzed and computerized for 60 of the finishers (Table 2). When pooled across treatment groups, there are significant increases in fat-free mass and BMD of femoral regions and significant decreases in body weight and fat mass. These preliminary findings indicate that the exercise program is sufficient for generating an osteogenic response, which is critical for determining whether the response is attenuated by NSAID use. At this stage of the project, all indications are that the study is progressing as planned.

A goal of year 3 of the study was to continue assays of biochemical markers of bone turnover and sex hormones. All samples for an individual study participant are being analyzed in batch. Serum concentrations of sex hormones, gonadotropins, and markers of bone turnover for 39 finishers are reported in Table 3. The values represent samples acquired during the month before and the final month of the exercise intervention, from the early follicular phase and the luteal phase (2 samples) of the menstrual cycle. These data have not been subjected to statistical analyses.

Table 4 presents a summary of dietary records and measurements of maximal oxygen consumption (VO_2max). These data indicate that energy and nutrient intake are remaining constant over the period of study and that the exercise program is sufficiently intense to generate a significant increase in VO_2max.

KEY RESEARCH ACCOMPLISHMENTS:

Consistent with the Statement of Work, the investigators remain blinded to treatment status for all participants. Therefore, there are no treatment-specific study results to report. The key accomplishments to date have been recruiting, completion of enrollment, and testing subjects, and continuing work on hormone and biomarker assays.

REPORTABLE OUTCOMES:

none

CONCLUSIONS:

Conclusions cannot yet be drawn because the investigators remain blinded to treatment status.

REFERENCES:

none

APPENDICES:

Figure 1. Study participant flow chart

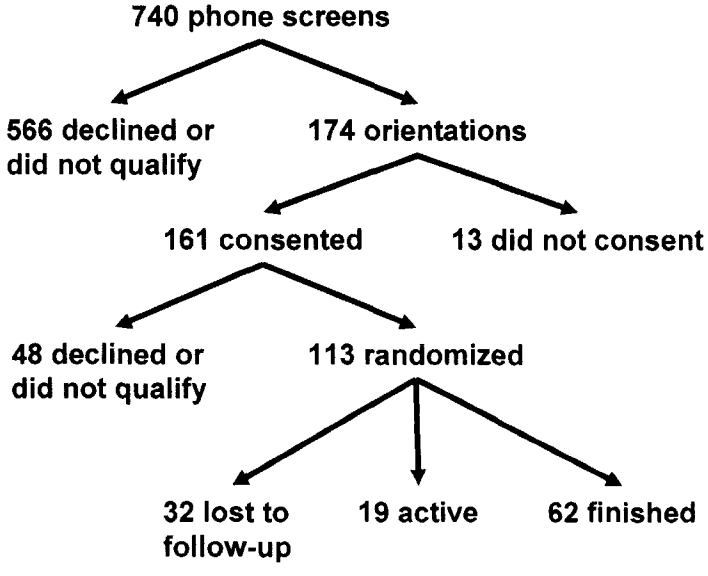

Table 1. Projected and actual enrollment by ethnicity and race

Race/Ethnic Category	Actual Current Enrollment	% Total	Projected Total Enrollment	% Total
RACE				
American Indian/ Alaskan Native	3	2	1	1
Asian	3	2	3	3
Native Hawaiian/Other Pacific Islander	0	0	0	0
Black/African American	2	2	6	6
White	99	89	92	90
Other/Hispanic	6	5	0	0
Total	**113**		**102**	
ETHNICITY				
Hispanic	15	13	20	20
Non-Hispanic	98	87	82	80
Total	**113**		**102**	

Table 2. Body composition and bone mineral density (BMD) of 60 finishers before and after 9 months of exercise training.

	before	after	change	p value
Age, yr	33 ± 5			
Height, cm	165 ± 8			
Weight, kg	65.5 ± 8.8	64.3 ± 8.0	-1.2 ± 2.5	**<0.001**
Fat-free mass, kg	44.1 ± 4.8	44.7 ± 4.7	0.6 ± 1.3	**<0.001**
Fat mass, kg	21.4 ± 6.0	19.6 ± 5.5	-1.8 ± 2.2	**<0.001**
BMD, g/cm^2				
total body	1.152 ± 0.100	1.159 ± 0.099	0.007 ± 0.019	**0.008**
lumbar spine	1.100 ± 0.134	1.106 ± 0.133	0.005 ± 0.025	0.089
total hip	0.987 ± 0.116	0.992 ± 0.112	0.005 ± 0.017	**0.028**
femoral neck	0.892 ± 0.124	0.894 ± 0.127	0.001 ± 0.027	0.702
trochanter	0.753 ± 0.103	0.758 ± 0.103	0.005 ± 0.017	**0.028**
femoral shaft	1.155 ± 0.136	1.164 ± 0.131	0.009 ± 0.027	**0.012**

Table 3. Sex hormone profiles and markers of bone turnover (N=33) measured in the early follicular phase (EFP) and twice during the luteal phase (LP1, LP2) of the menstrual cycle before and after exercise training.

	before			**after**		
	EFP	LP1	LP2	EFP	LP1	LP2
E_2, pg/mL	59 ± 26	102 ± 92	92 ± 66	61 ± 20	88 ± 71	88 ± 61
P_4, ng/mL	0.42 ± 0.15	4.4 ± 4.5	4.7 ± 4.8	0.5 ± 0.3	3.6 ± 4.4	3.9 ± 4.6
SHBG, nmol/L	284 ± 156	320 ± 202	310 ± 190	271 ± 152	301 ± 180	306 ± 175
FSH, IU/L	3.4 ± 3.2	1.7 ± 1.6	1.8 ± 2.8	2.9 ± 1.4	1.9 ± 1.8	1.8 ± 2.0
LH, IU/L	5.2 ± 3.4	7.4 ± 9.5	4.1 ± 4.5	5.0 ± 3.5	4.3 ± 3.2	4.2 ± 3.8
CTx, ng/mL	0.43 ± 0.23	0.37 ± 0.21	0.37 ± 0.22	0.48 ± 0.28	0.37 ± 0.16	0.42 ± 0.23
BAP, U/L	22.6 ± 7.0	22.9 ± 7.8	23.2 ± 8.0	23.8 ± 7.4	23.2 ± 7.2	21.7 ± 6.5

E_2=estradiol; P_4=progesterone; SHBG=sex hormone-binding globulin; FSH=follicle stimulating hormone; LH=luteinizing hormone; CTx=C-terminal telopeptide of type I collagen (bone resorption marker); BAP=bone-specific alkaline phosphatase (bone formation marker)

Table 4. Dietary intake and cardiovascular fitness before and after 9 months of exercise training.

	before	**after**	**change**	**p value**
Energy intake, kcal/d	1865 ± 340	1762 ± 381	-104 ± 380	0.5931
protein, g/d	76 ± 18	74 ± 19	-1 ± 18	0.4366
carbohydrate, g/d	227 ± 51	221 ± 53	-6 ± 60	0.4302
fat, g/d	71 ± 18	64 ± 21	-7 ± 20	0.2794
Calcium intake, g/d	932 ± 294	940 ± 407	9 ± 445	0.5845
VO_2max, mL/min/kg	32.7 ± 4.7	36.5 ± 5.2	3.7 ± 3.5	**<0.001**
HRmax, beats/min	188 ± 10	185 ± 9	-3 ± 7	**0.002**

VO_2max=maximal aerobic power; HRmax=maximal heart rate